Cystic Fibrosis our focus

The *Burkholderia cepacia* complex.
Suggestions for Prevention and Infection Control

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Fighting for a Life Unlimited

The UK Cystic Fibrosis Trust Infection Control Group

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The *Burkholderia cepacia* complex

Suggestions for Prevention and Infection Control Report of the UK Cystic Fibrosis Trust Infection Control Group

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Preface

In 1999, the UK Cystic Fibrosis Trust Infection Control Group produced a document A statement on Burkholderia cepacia. In light of information from recently published studies and a new taxonomy for the *B. cepacia* complex, the UK Cystic Fibrosis Trust Infection Control Group has now extensively revised the original document.

The present document reviews much of the available information on the prevention and control of *B. cepacia* complex infection in people with cystic fibrosis (CF). Some of the recommendations in this document are based on firm evidence and many on experience. The recommendations are considered to represent best practice for the prevention and control of *B. cepacia* complex infection with the present state of our knowledge; it is hoped that they may serve to provide some guidance for local policies. It is intended that the present recommendations will be revised every two years to take account of new developments.

Regular expert microbiological surveillance of people with CF is recommended if spread of a transmissible organism amongst patients is to be identified and dealt with at an early stage. For this, expert microbiological laboratory services are required by the clinic. The reference laboratories mentioned in the document are prepared, after discussion, to examine cultures from Specialist CF Centres and CF Clinics who wish to confirm whether they have a *B. cepacia* complex isolate and whether this may be a known cross-infecting strain.

Finally, the ultimate responsibility for the infection control policy in an individual clinic lies with the clinic director and staff in consultation with their microbiologist and their hospital infection control committee; together they can decide on the precise precautions that are appropriate and necessary in their particular clinic.

The UK Cystic Fibrosis Trust Infection Control Group
September 2004

Grading scheme for recommendations used in the *Burkholderia cepacia* complex

The criteria for the grading of recommendations in this document are based upon a paper by Petrie et al published on behalf of the Scottish Intercollegiate Guidelines Network.

Much of the data in the document are derived from observational studies where randomisation is not appropriate or possible, but many are from peer-reviewed scientific studies therefore this grading is not always appropriate.

Levels of evidence

Level	Type of evidence (based on AHCPR, 1992)
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well designed controlled study without randomisation.
IIb	Evidence for at least one other type of quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of recommendations

Grade	Type of recommendation (based on AHCPR, 1992)
A (levels Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of the recommendation.
C (level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

Petrie GJ, Barnwell E, Grimshaw J, on behalf of the Scottish Intercollegiate Guidelines Network. Clinical guidelines: criteria for appraisal for national use. Edinburgh: Royal College of Physicians, 1995.

Agency for Health Care Policy and Research. Acute pain management, operative or medical procedures and trauma 92- 0032. Clinical practice guidelines. Rockville, Maryland, USA: Agency for Healthcare Policy and Research Publications, 1992.

Summary

This is a summary of the recommendations of the UK Cystic Fibrosis Trust Infection Control Group to reduce the possibility of people with cystic fibrosis (CF) transmitting from person to person the bacteria of the Burkholderia cepacia complex (Bcc), which includes Burkholderia cenocepacia. The document contains up-to-date information about Bcc and how these bacteria can affect people with cystic fibrosis. It also gives advice to help reduce the risk of people with CF catching these bacteria from each other. Because Bcc bacteria can be acquired during activities where people with CF meet together outside the hospital, this statement describes what we know about the relative risks of various kinds of activity.

The most important points are listed below but please refer to the full document for more detailed information.

- People with CF who have Bcc infection have more problems with their chest and some become very ill - so it is better to prevent infection with these bacteria. Some people with CF contract Bcc infection and remain quite stable.
- Bcc bacteria do not usually cause infection in healthy people.
- All people with CF should know which bacteria they have in their sputum, and sputum should be checked (cultured) regularly at the Specialist CF Centre or CF Clinic.
- Bcc affects only a minority of people with CF and is mostly caused by passing the infection from person to person.
- Close contact such as sharing rooms, sharing nebuliser equipment, kissing or coughing close to another person with CF are activities which are high risk for passing bacteria from person to person.

- Cross-infection can be significantly reduced by keeping people with CF who are infected with Bcc bacteria apart from others with CF, not only in hospital but also outside of hospital, and by careful attention to good hygiene such as hand washing.
- People with Bcc infection should not attend meetings where there are other people with CF and should not mix with other people with Bcc who may be carrying a different type of Bcc bacteria.
- Unfortunately, there is still a great deal we do not know about Bcc bacteria, and this document cannot hope to cover everybody's individual circumstances. If you have further questions about Bcc bacteria please discuss them with staff at the Specialist CF Centre or CF Clinic or contact the Cystic Fibrosis Trust.

1. Historical perspective

In the late 1970s and early 1980s, an increasing incidence and prevalence of Burkholderia cepacia isolates was reported in North American CF Centres (Isles et al, 1984 [III]; Thomassen et al, 1985 [III]). Those people with CF with B. cepacia infection were noted to have an increased morbidity and mortality (Tablan et al, 1985 [III] and 1987 [III]; Muhdi et al, 1996 [III]). Subsequent studies using molecular fingerprinting techniques established compelling evidence of cross-infection, including direct patient-to-patient spread via contacts within Specialist CF Centres and outside of clinics through social contacts (LiPuma et al, 1990 [III]; Govan et al, 1993 [III]; Smith et al, 1993 [III]; Millar-Jones et al, 1992 [III]; Cazzola et al, 1996 [III]; Pegues et al, 1994a and 1994b [III] Millar-Jones et al, 1998 [III]). However, a review of 23 published studies (Govan et al, 1996 [IV]) showed that cross-infection was not inevitable, even in the case of siblings with CF, suggesting that spread might be strain-dependent.

The introduction of strict segregation policies led to a dramatic fall in incidence of cross-infection at Specialist CF Centres (Thomassen et al, 1986 [III]; Muhdi et al, 1996 [III]). A longitudinal case- controlled study in Mississippi covering the period 1988-1993 demonstrated that B. cepacia could be transmitted between patients with and without cystic fibrosis (Holmes et al, 1999 [III]). The observation that existing *B. cepacia* infection could be replaced with more virulent and transmissible strains further influenced the cohorting of *B. cepacia*–positive people. Transmission however did not appear to be inevitable since several contemporary studies found no evidence of cross-infection (Glass & Govan, 1986 [III]; Hardy et al, 1986 [III]; Taylor et al, 1992 [III]; Steinbach et al, 1994 [III]). In 1997 a seminal taxonomic study revealed that isolates previously identified as *B. cepacia* comprised a complex of multiple closely related species or genomovars (Vandamme et al, 1997 [III]).

2. Taxonomy of the *Burkholderia cepacia* complex

Since 1997, the taxonomy of *B. cepacia* has undergone major revisions. The use of polyphasic analyses including DNA/DNA hybridization, whole cell protein analyses (Vandamme et al, 1997 [III]) and later recA polymerase chain reaction (PCR) (Mahenthiralingam et al, 2000a [III]; Vermis et al, 2002 [III]) have shown that organisms previously identified as *B. cepacia* comprise multiple distinct but closely related genomic species, or genomovars. As a group, these bacteria are referred to as the *B. cepacia* complex. Currently 9 genomovars of the *B. cepacia* complex have been described (Coenye et al, 2001a [III]). To comply with the rules of taxonomic nomenclature, genomovar I retains the original designation of "*B. cepacia*"; other Bcc members are then provided with new or previously designated species names as appropriate. For the purpose of this document, the term Bcc will be used to refer to Bcc collectively, and to describe isolates referred to as "*B. cepacia*" prior to 1997.

Burkholderia cepacia complex

Genomovar I . . . . . .Burkholderia cepacia
Genomovar II . . . . . .Burkholderia multivorans
Genomovar III (a, b, etc) . . . .Burkholderia cenocepacia
Genomovar IV . . . . . .Burkholderia stabilis
Genomovar V . . . . . .Burkholderia vietnamiensis
Genomovar VI . . . . . .Burkholderia dolosa
Genomovar VII . . . . . .Burkholderia ambifaria
Genomovar VIII . . . . . .Burkholderia anthinia
Genomovar IX . . . . . .Burkholderia pyrrocinia

3. Clinical consequences of *Burkholderia cepacia* complex infection in people with cystic fibrosis

Burkholderia cepacia complex infection is associated with an increased morbidity and shortened life-expectancy for people with cystic fibrosis. However some people with Bcc remain stable for many years and in some the infection may be transient (Govan et al, 1996 [IV]). It is important to note, however, that clinical outcome varies even in patients infected with the same cluster strain, including the intercontinental strain ET12 (Govan et al, 1993 [III]), and the unique Australian Hunter strain (Fitzgerald et al, 2001 [III]). Clinical outcome is also variable in patients infected with subgroups of the *B. cepacia* complex (Soni et al, 2002 [III]).

- Isles et al, reported 7 deaths in 18 patients with Bcc infection, compared with 4 deaths in 67 patients without *B. cepacia* infection, although the Bcc-positive patients were older and had worse lung function (Isles et al, 1984 [III]).

- In Vancouver patients with Bcc infection were more likely to be hospitalised for longer and died sooner than controls (Tablan et al, 1985 [III]).
- In Cleveland paediatric patients with Bcc infection had a decreased survival in comparison to Bcc-negative patients matched by Shwachman clinical scores; this was particularly so for patients with moderate or advanced lung disease who then acquired B. cepacia infection (Tablan et al, 1987 [III]).
- In Birmingham UK, the number of inpatient days and outpatient visits increased following acquisition of Bcc infection in comparison with controls; 61% of patients with Bcc infection died compared with 31% of controls (Muhdi et al, 1996 [III]).
- Frangolias et al compared patients with and without Bcc infection matched by age, sex, pancreatic status and respiratory function (FEV1 percent predicted). At long-term follow- up, the Bcc-negative patients had a significant survival advantage (Frangolias et al, 1999 [III]).
- In the Canadian CF Registry data, *B. cepacia* was associated with increased mortality at all levels of pulmonary function (Corey & Farewell, 1996 [III]).
- Patients with the highly transmissible *B. cenocepacia* strain ET12 (belonging to genomovar IIIa) were shown to have a fourfold risk of mortality greater than those with Pseudomonas aeruginosa infection who attended the same UK Specialist CF Centre (Ledson et al, 2002 [III]).
- In Vancouver, 20 of 46 patients with *B. cenocepacia* infection died in comparison with only 3 of 19 with *B. multivorans* infection. Furthermore, 2 of the latter 3 patients were subsequently superinfected with *B. cenocepacia* before they died (Mahenthiralingam et al, 2001 [III]).
- In Sydney, an actuarial survival study of 15 Bcc-infected patients found that infection had a significant adverse effect on survival with a mortality rate of 40% compared with 17% for the entire clinic population (Soni et al, 2002 [III]).

3.1 Lung Transplantation

- One-year post-transplant survival for people with CF was 67% for Bcc-infected patients and 92% for Bcc-negative patients at a North American Centre (Chaparro et al, 2001 [III]).
- At a UK transplant centre, 5 of 11 patients with Bcc infection died post-transplant because of progressive Bcc-related related sepsis; the 4 isolates that were available for genomovar analysis were all found to be *B. cenocepacia* and were a single strain, namely ET12. None of the 5 available Bcc complex isolates from the 6 patients who survived were *B. cenocepacia* (De Soyza et al, 2001 [III]).
- There was a significant excess mortality for patients with CF infected pre-operatively with Bcc than those not infected (33% v 12%). Patients with B. cenocepacia infection were at the highest risk of death: 5 of 12 died in comparison with 0 of 8 for other Bcc genomovars. An important observation in this study was that each *B. cenocepacia* death was caused by a unique genotype indicating that increased mortality was related to the species rather than a particular strain (Aris et al, 2001 [III]).
- Modifications to surgical and peri-transplant therapy may improve the outcome in Bcc- infected people with CF, including those infected with *B. cenocepacia* ET12 (Chaparro et al, 2001 [IV]; De Soyza et al, 2001 [IV]; De Soyza et al, 2004 [IV]).

3.2 Cepacia syndrome

- Isles et al first described a syndrome of a fulminant pneumonia in association with Bcc infection characterised by high fever, leucocytosis, sepsis and severe progressive respiratory failure (Isles et al, 1984 [III]; Tablan et al, 1985 [III]). Although Isles et al did not specifically use the term, this rapid and life-threatening outcome of Bcc infection, with a particularly poor prognosis, has become known as ‘cepacia syndrome’.
- Although thought to be primarily associated with *B. cenocepacia* strains, cepacia syndrome can occur with *B. multivorans* and other members of the *B. cepacia* complex (Mahenthiralingam et al, 2001 [III]; Jones & Webb, 2003 [III]).

Summary

Previous clinical studies have shown that Bcc infection is associated with an increased morbidity and mortality for people with cystic fibrosis. The relative virulence of individual Bcc species, and strains within a species, remains unclear. However evidence suggests that *B. cenocepacia* is the species with the greatest potential virulence for people with cystic fibrosis. Decreased survival of Bcc patients post-transplantation seems particularly associated, though not exclusively, with prior *B. cenocepacia* infection. Modifications to surgical and peri- and post-transplant medical therapy may improve outcome for this group of patients. People with *B. cenocepacia* and *B. multivorans* should still be considered for transplantation but in the light of other risk factors.

4. Cross-infection control

The risk of Bcc cross-infection, caused by direct or indirect contacts, is related to a number of factors, including patient behaviour, infection control practices and the particular Bcc species and strains involved.

- The emergence and spread of highly transmissible Bcc strains (sometimes referred to as lineages) resulted in an increase in the incidence and prevalence of *B. cepacia* infection at many Specialist CF Centres during the past two decades. The spread, at national and intercontinental level, of the *B. cenocepacia* strain ET12 (Govan et al, 1993 [III]; Johnson et al, 1994 [III]; Govan et al, 1996, [IV]; Pitt et al, 1996 [III]) has strongly influenced Bcc epidemiology. This factor provides an important caveat in attempts to generalise on Bcc issues. What is certain is the compelling evidence of the spread of transmissible strains within and between Specialist CF Centres (Govan et al, 1993 [III]; Smith et al, 1993 [III]; Johnson et al, 1994 [III]; Whiteford et al, 1995 [III]; Segonds et al, 1997 [III]; Govan et al, 1996 [IV]).
- There is also compelling evidence for patient-to-patient spread of Bcc outside Specialist CF Centres, CF Clinics and hospitals e.g. through attendance at summer camps and other forms of regular social contact (LiPuma et al, 1990 [III]; Govan et al, 1993 [III]; Smith et al, 1993 [III]; Pegues et al, 1994a [III]).
- Individual host factors, including polymorphisms in mannose binding lectins may affect susceptibility to Bcc infection (Garred et al, 1999 [III]; Davies et al, 2000 [III]).
- The introduction of strict segregation policies by Specialist CF Centres has helped to limit *B. cepacia* cross-infection (Thomassen et al, 1986 [III]; Govan et al, 1993 [III]; Muhdi et al, 1996 [III]; Govan, 2000 [IV]). It is important to note that segregation does not eliminate entirely the risk of Bcc acquisition from natural environmental reservoirs.
- In the early 1990s, Bcc-positive patients were cohorted together irrespective of Bcc strain involved. Subsequently, superinfection, in which a new strain replaces an existing Bcc strain, was reported. One UK Specialist CF Centre reported 5 cases in which *B. cenocepacia* ET12 replaced existing Bcc strains with serious consequences; 4 patients subsequently died, 3 from cepacia syndrome (Ledson et al, 1998 [III]).
- In Vancouver, 6 cases of superinfection occurred before species-dependent segregation was introduced. *B. cenocepacia* strains replaced *B. multivorans* with worsening of the clinical condition of the patient (Mahenthiralingam et al, 2001 [III]). The clinical relevance of superinfection appears to be influenced by the Bcc species and strain involved. Pulmonary exacerbations with Bcc and Pseudomonas aeruginosa are no more severe than when only Bcc was isolated (McManus et al, 2003 [III]).

Summary

Although it causes considerable anxiety and psychosocial consequences, segregating Bcc-positive patients has reduced the spread of highly transmissible Burkholderia cepacia complex. Segregation cannot however prevent occasional acquisition of Bcc from the natural environment. The risk of superinfection has highlighted the need to extend cohort segregation of people with CF with Bcc to take account of the species and strain involved.

5. General environment and *Burkholderia cepacia* complex

Stringent infection control policies have helped to limit cross-infection, but have not eliminated entirely the risk of sporadic acquisition of Bcc from natural environmental reservoirs. In the absence of human commensal carriage of Bcc, it is often assumed that sporadic cases of Bcc infection occur following contact with an environmental source. This is probably true; however, it is difficult to provide unequivocal evidence for this assumption.

- The precise environmental niches of Bcc thought to be responsible for human infections, including those in people with CF, are unclear. The natural habitats of Bcc species are soils, the plant rhizosphere (the region of soil in the vicinity of plant roots) and freshwater environments such as river sediments (Fisher et al, 1993 [III]; Butler et al, 1995 [III]; Balandreau et al, 2001 [III]; Fiore et al, 2001 [III]; Miller et al, 2002[III]; Vermis et al, 2003 [III]). Early studies reported low isolation rates for Bcc from a range of natural environments (Butler et al, 1995 [III]; Fisher et al, 1993 [III]). However, the use of improved selective culture has shown that Bcc bacteria are relatively common in such environments (Balandreau et al, 2001 [III]; Fiore et al, 2001 [III]; Miller et al, 2002 [III]; Vermis et al, 2003 [III]). There is also evidence of a close relationship between environmental and clinical isolates. The use of genomic fingerprinting demonstrated a clonal relationship between a plant isolate of B. cepacia and an isolate from a person with cystic fibrosis (Govan et al, 2000 [IV]); also a highly transmissible B. cenocepacia strain has been identified in soil samples from a field in the USA (LiPuma et al, 2002 [III]).
- Burkholderia multivorans is rarely isolated from the natural environment but is one of the two most common Bcc species in isolates from CF sputum

(Agodi et al, 2001 [III]; Mahenthiralingam et al, 2002 [III]).

- Burkholderia cepacia complex bacteria were rarely isolated in an environmental screening study of a hospital CF ward (Doring et al, 1996 [III]).
- Burkholderia cepacia complex bacteria were isolated in only 5 of 916 isolates cultured from homes of people both with and without cystic fibrosis (Mortensen et al, 1995 [III]).
- Burkholderia cepacia complex was isolated from 3 of 35 home-use nebulisers. Patients who followed recommended instructions for good nebuliser hygienic practice and paid particular attention to drying had minimal or no contamination of their nebulisers. Of the three cases where Bcc was cultured from a nebuliser, in only one case was the same strain present in the sputum of that patient (Hutchinson et al, 1996 [III]).
- Burkholderia cepacia complex can survive on skin for up to 30 minutes, on sputum- contaminated surfaces for weeks and in distilled water for many years (Govan, 2000 [IV]). Strain-to-strain differences in survival have also been demonstrated (Drabick et al, 1996 [III]).
- An air sampling study showed the presence of Bcc in room air in 5 of 6 rooms occupied by Bcc-positive people with cystic fibrosis. Bcc persisted in room air on 4 occasions after the patient left the room; on one occasion for up to 45 minutes (Humphreys et al, 1994 [III]). A further study showed that air samples were more likely to be Bcc-positive after airway clearance (47%) than before (16%) (Ensor et al, 1996 [III]).

Summary

Although Bcc has been isolated from various environmental sources the risk of acquisition from the general environment is low.

6. Transmissibility markers

- Accumulated evidence suggests that transmissibility of Bcc organisms is influenced by strain and species. Most previous Bcc outbreaks have been associated with B. cenocepacia, and the ET12 strain in particular (Govan et al, 1996 [IV]; Mahenthiralingam et al, 2001 [III]). However, cross-infection involving B. multivorans and other genomovars has also been reported (Whiteford et al, 1995 [III]; Agodi et al, 2001 [III]; Mahenthiralingam et al, 2002 [III]; Segonds et al, 1999 [III]).
- The well-described transmissible *B. cenocepacia* strain, ET12, possesses a gene (cblA) that encodes for the major structural subunit of cable-like and mucin binding pili (Sun et al, 1995 [III]). A DNA marker, known as Burkholderia cepacia epidemic strain marker (BCESM), has also been identified in a number of transmissible *B. cenocepacia* strains (Mahenthiralingam et al, 1997 [III]; Baldwin et al, 2004 [III]). BCESM and cblA are not found in all transmissible Bcc strains (Agodi et al, 2001 [III]; LiPuma et al, 2001 [III]) and their absence does not equate with lack of transmissibility. Burkholderia cenocepacia ET12 appears to be unique in possessing both markers.

Following accurate laboratory identification, genomic fingerprinting of Bcc to identify strain relationships is a major requirement for epidemiological studies and for infection control surveillance. At present pulsed-field gel electrophoresis (PFGE) is the gold standard. In future, PFGE may be augmented or replaced by multilocus sequence typing.

7. Transient infection

Some people with cystic fibrosis may acquire transient infection with Bcc but it is more common with *B. multivorans* and other Bcc species than with *B. cenocepacia* (Mahenthiralingam et al, 2001 [III]; Jones & Webb, 2003 [IV]).

When a patient can be declared free of infection, and therefore potentially allowed to mix with other Bcc-negative people with CF, can be a difficult clinical dilemma.

Recommendations

- Before a person with CF can be considered as being free from Bcc there should be evidence of at least 3 negative sputum cultures over a period of at least one year [C].
- Until considered free of infection patients should remain segregated from other people with cystic fibrosis [C].

8.Summary of present clinical knowledge of individual *Burkholderia cepacia* complex species

In CF Centres in Europe and North America, there is a variable prevalence of Bcc species (Agodi et al, 2001 [III]; LiPuma et al, 2001 [III]; Mahenthiralingam et al, 2002 [III]; Speert et al, 2002 [III]; Drevinek et al, 2002 [III]). Approximately 90% of Bcc isolates from CF sputum can be identified as

B. multivorans and *B. cenocepacia*. The clinical significance of individual species within the Bcc is still largely unknown. Whilst most transmissible strains belong to *B. cenocepacia*, cross-infection outbreaks relating to other Bcc species, in particular *B. multivorans* have been reported in people with cystic fibrosis (Whiteford et al, 1995 [III]; Segonds et al, 1999 [III]; Agodi et al, 2001 [III]).

8.1 *Burkholderia cenocepacia*

- Is one of the most common Bcc species isolated from CF sputum.
- Can be isolated from the natural environments, particularly agricultural soil.
- The majority of Bcc strains associated with cross-infection between people with CF are *B. cenocepacia* strains.
- Cepacia syndrome is more commonly associated with *B. cenocepacia* than other Bcc species.
- With the exception of post-transplantation outcome, it is unclear whether the apparent increased virulence of *B. cenocepacia* amongst Bcc is species and strain dependent. Further data are required to assess the potential virulence of those Bcc species with low prevalence.
- Prior infection with *B. cenocepacia* is strongly associated with a poor post-transplantation outcome (Chaparro et al, 2001 [IV]; De Soyza et al, 2001 [IV]); this appears to be species rather than strain specific (Aris et al, 2001 [IV]). There is evidence that modifications to the peri-transplant surgical and medical care improves the outcome for patients with
- *B. cenocepacia* infection, including infection with the ET12 strain (De Soyza et al, 2001 [IV]; De Soyza et al, 2004 [IV]).

8.2 *Burkholderia multivorans*

- Is rarely isolated from natural environments but is one of the most common Bcc species isolated from CF sputum.
- UK microbiological surveillance shows that most new cases of *B. multivorans* infection are caused by unique genotypic strains suggesting sporadic acquisition from natural environments (Turton et al, 2003 [III]). Outbreaks of *B. multivorans* cross-infection among people with CF are less frequent than with *B. cenocepacia* but have been described (Whiteford et al, 1995 [III]; Segonds et al, 1999 [III]; Agodi et al, 2001 [III]; Mahenthiralingham et al, 2002 [III]).
- Evidence suggests that the potential for virulence in *B. multivorans* is less than that in *B. cenocepacia*; however, *B. multivorans* can occasionally cause cepacia syndrome (Mahenthiralingam et al, 2001 [III]; Jones & Webb, 2003 [III]).

8.3 Other *Burkholderia cepacia* complex species

- All have been isolated from CF sputum specimens (Mahenthiralingam et al, 2002 [III]).
- Cross-infection outbreaks have been Reported with other Bcc species including *B. pyrrocinia* (Campana et al, 2003 [III]).
- At present, there is insufficient evidence to draw firm conclusions as to the relative pathogenicity of other Bcc species.

9. Other non-*Burkholderia cepacia* complex burkholderia species

9.1 *Burkholderia gladioli*

- The clinical significance of *B. gladioli* infection in people with cystic fibrosis remains unclear. The first report (Wilsher et al, 1997 [III]) of an adverse clinical outcome following colonisation with *B. gladioli* had to be revised when the organism was subsequently identified as *B. cenocepacia* ET12 (Clode et al, 1999 [III]). *Burkholderia gladioli* can cause chronic infection in people with CF, although the prevalence is thought to be low (Wilsher et al, 1997 [IV]; Barker et al, 1997 [IV]; Jones et al, 2001a [IV]).
- There are currently no published reports of cross-infection with *B. gladioli* among people with cystic fibrosis.

9.2 *Burkholderia mallei* and *Burkholderia pseudomallei*

- Burkholderia mallei and *B. pseudomallei* are closely related to the Bcc and are important human pathogens, requiring 'handling' under laboratory category III containment. *Burkholderia mallei* is the agent of equine glanders and is highly virulent in humans; fortunately such infections are extremely rare. *Burkholderia pseudomallei* is the causative agent of melioidosis, a life-threatening human infection found during the rainy season predominantly in the subtropical regions of Southeast Asia and Australia.
- Cases of *B. pseudomallei* infection in people with CF visiting Southeast Asia have been described, in some cases involving co-infection with *B. cepacia* complex (Schulin & Steinmetz, 2001 [III]; Visca et al, 2001 [III]); cases have also been described in New Zealand (Holland et al, 2002 [IV]) and Australia (O'Carroll, et al, 2003 [IV]).

Recommendations

- Cystic fibrosis clinicians and microbiologists should be aware of the possibility of B. pseudomallei infection in people with CF returning from South East Asia where theorganism is endemic [B].
- Travelling to such places during the rainy season, when the organisms can be present in soil in high numbers, is not advised for people with cystic fibrosis [B].

10. Laboratory identification of *Burkholderia cepacia* complex

Accurate identification of Bcc from specimens of sputum from people with CF is of the utmost importance. False positive identification has serious psychological, social and organisational consequences; these include exclusion from scientific conferences and social events or rejection as a potential lung transplant recipient. False negative identification could affect the CF community at large by leading to epidemic spread (Miller & Gilligan, 2003 [IV]).

In the clinical microbiology laboratory, the use of selective media and appropriate identification procedures is vital for optimum culture and reliable diagnosis of Bcc in sputum and other clinical specimens (van Pelt et al, 1999 [III]; Miller & Gilligan, 2003 [IV]). Identification of Bcc by common commercial systems is unreliable. When a Bcc strain panel (Mahenthiralingam et al, 2000b [III]) was used to evaluate various commercial systems, API 20NE proved to be the most accurate (Govan unpublished data); it was also the only system that identified B. cenocepacia ET12 and the *B. multivorans* strain responsible for a serious outbreak in a paediatric Specialist CF Centre (Whiteford et al, 1995 [III]).

- An initial report described cross-infection with B. gladioli at a Specialist CF Centre (Wilsher et al, 1997 [III]). It was subsequently shown the species had been misidentified and was in fact *B. cenocepacia* ET12 (Clode et al, 1999 [III]).
- 88 (11%) of 770 CF isolates from 115 US CF Centres sent to the CF Foundation *Burkholderia cepacia* Research Laboratory and Repository, that had been provisionally identified by referring laboratories as Bcc, were found to have been misidentified. Of a further 281 isolates not specifically identified or identified as another species, 101 (36%) were found to be *Burkholderia cepacia* complex (McMenamin et al, 2000 [III]).
- 34 (12%) of 282 CF isolates from 19 UK Specialist CF Centres sent to the Edinburgh CF Microbiology Laboratory and Strain Repository as Bcc were misidentified. False- negatives were rare, with only one isolate (referred as *Pseudomonas aeruginosa*) identified as *Burkholderia cepacia* complex (Govan unpublished data).

Infection control strategies and laboratory identification for Bcc require an awareness of the problems that may arise in culture and identification, including the

consequences of recent taxonomic research pioneered by Peter Vandamme in Gent, Belgium (Vandamme et al, 1997 [IV]). Unless state-of-the-art facilities are available on site, all new isolates suspected as Bcc should be sent to a referral laboratory experienced in the phenotypic and DNA-based identification of the group. To ensure optimum culture and identification of the *B. cepacia* complex from CF respiratory secretions it is essential to use selective media** and incubate at 37°C for at least 72 hours. Bacterial colonies tentatively identified as Bcc can be further identified by a multitest commercial system (e.g. API 20NE). The single tube arginine glucose medium provides a simple, inexpensive and reliable screen to reduce the number of false positives after isolation from Bcc selective media, and is particularly useful when large numbers of isolates require investigation (Govan, 1996 [III]). Further tests available on request to National Referral Laboratories at Colindale and Edinburgh*** include identification of individual Bcc species based on specific phenotypic tests and recA-based polymerase chair reaction (PCR). PCR identification of epidemic markers (BCESM and cblA) is also available as well as genomic fingerprinting (RAPD, PFGE, MLRT) to investigate clonality of individual isolates for infection control surveillance and other studies.

** See below for details.

*** See below for details.

**Recommended selective culture media:

Mast cepacia agar: Mast Group Ltd, Bootle, UK. L20 1EA
Burkholderia cepacia selective agar (BCSA) (Henry et al, 1997 [III]).

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11. Treatment – recent advances

Antibiotic susceptibility patterns are strain dependent and strains often exhibit multi-resistance (Nzula et al, 2002 [III]). Treatment should be based on antibiotic sensitivity patterns where these are available and will often involve the use of multiple antibiotics, the choice of which may be aided by synergy testing which is being evaluated (Aaron et al, 2000 [III]; Antibiotic Treatment for Cystic Fibrosis. Cystic Fibrosis Trust, 2002 [IV]).

At present, there are no published studies describing regimens for the eradication of early Burkholderia cepacia complex infection. A preliminary report using a combination of nebulised amiloride and tobramycin successfully eradicated the organism in 3 of 4 patients (Middleton & Williams, 2004 [IV]).

12. Recommendations to limit spread

There is compelling evidence that people with CF can acquire Bcc by direct patient-to-patient spread in hospital or during social contacts outside hospital or occasionally via acquisition from contaminated environments. Following the introduction of effective infection control measures most new infections are now with sporadic strains. Current medical opinion is that patients with CF with Bcc infection should be segregated from each other and all other people with cystic fibrosis.

Regular attendance and follow-up at a Specialist CF Centre has been shown to be beneficial to both children and adults (Mahadeva et al, 1998 [III]). Therefore avoiding clinic attendance because of fear of Bcc infection is likely to be harmful in that it may seriously interfere with medical care and far outweigh any potential risk of acquiring new infection - provided adequate infection control measures are in place.

12.1 General

- Patients and carers should be encouraged to discuss their concerns about infection control measures with the clinic staff [C].

12.2 Segregation of patients according to their microbiological status

- Every Specialist CF Centre and CF Clinic, large or small should have a surveillance and infection control policy that considers cross-infection risk [B].
- The methods used and extent to which Specialist CF Centres and CF Clinics segregate patients should be determined by local policy based on knowledge of the patient's microbiological status [C].
- Good hygiene should be practiced in all outpatient clinics and inpatient facilities to minimise the risk of transmission of Bcc between patients [B].
- Regular microbiological surveillance should include specific examination for Bcc organisms. An increase in incidence of Bcc isolations would suggest the presence of a transmissible strain [B].
- A policy of segregation should cover both inpatient admissions and outpatient clinics. There should be separate clinics for patients chronically infected with Bcc and those who are Bcc- negative [C].
- The Bcc clinics should be held on different days or at a later session to avoid patients meeting and mixing in other departments e.g. laboratory, pharmacy, X-ray, restaurant etc [C].
- Bcc patients should be seen in different Bcc clinics according to their genomovar status. Also those with highly transmissible strains and sporadic strains of the same genomovar should be seen separately [C].

12.3 In the outpatient clinic

Good hygienic measures are of great importance in any clinic. These should form part of the local infection control policy for the hospital, but the following are recommendations for best practice for those dealing with people with cystic fibrosis.

General hygienic measures to limit cross-infection

- Hand washing, disinfection with alcohol rubs or the use of disposable gloves before and after contact with each patient is recommended to minimise cross-infection [B].

• Patients should cover their mouths or noses when coughing or sneezing [B].

- Patients should wash or disinfect their hands before use of a spirometer or other handheld apparatus [B].
- Respiratory function tests should be performed in a well-ventilated room away from other patients [B].
- Local infection control policies should be established to prevent contamination and cross- infection from clinic equipment. This will depend on the nature of the equipment [C].
- Sputum specimens and throat swabs should be obtained in a well-ventilated room away from other patients [B].
- Sputum pots should be covered and soiled tissues must be disposed of immediately after use in the clinical waste bin. Sputum should not be expectorated down toilets, sinks, and washbasins or in showers [B].
- Airway clearance techniques should be carried out in a separate room away from the waiting area [B].
- The physiotherapists should take appropriate hygienic precautions to prevent contamination of their hands and clothing with respiratory secretions by the use of disposable aprons [B].
- Cleaning of surfaces and apparatus between patients should be specified by local infection control policies [C].
- Consideration should be given to the potential for possible cross-infection afforded by toys, books, magazines, computers, game consoles and other communal facilities [C].
- Patients with CF should be encouraged to bring their own toys and books and not share them with others with cystic fibrosis [C].
- All equipment should be cleaned and dried after use and maintained according to the local infection control policies [B].
- Apparatus, stethoscopes, sphygmomanometers, auroscopes etc. should be cleaned between patients [B].

12.4 Additional recommendations for inpatients

- All members of medical, paramedical, nursing and other staff who have physical contact with patients should practice hand washing or appropriate disinfection of hands between dealing with different patients. This includes anyone who comes into contact with the patient [C].
- Patients should have well-ventilated single rooms of an adequate size and there should be en suite facilities in all rooms [C].
- Respiratory function tests, exercise tests, nebulisation and physiotherapy treatment sessions should be carried out either separately in the physiotherapy department, a treatment room or in the patient's own room with the door closed [C].
- Patients should have their own nebuliser-compressor system, oxygen therapy delivery devices and airway clearance devices as required. Equipment should not be shared between patients [C].
- Sinks, taps and showers should be cleaned according to local infection control policies [C].
- Eating and drinking utensils and sweets should not be shared between patients [C].
- Food should be consumed in the patients' rooms rather than at a communal table [C].
- Rooms should be cleaned between patients according to local infection control policies [C].
- Grouping of children with CF for hospital schooling arrangements is no longer appropriate [C].
- Bcc patients should be nursed on different wards according to genomovar status, and on different wards to non-Bcc patients [B].

12.5 Away from the hospital

Casual meetings between people with CF, including brief encounters indoors and outdoors, carry a small risk of infection and this risk is increased the longer and closer the contact.

- Patients should discuss cross-infection issues with their physician and CF Team and be aware of their own microbiological status [C].
- All communal CF camps and holidays should be avoided [B].
- Spa and other forms of aerated baths should be avoided [B].
- Schooling: although there are a few reports that Bcc infection can be transmitted between children in the school environment, it is preferable for children with CF attending the same school to be in different classes; if possible they should attend different schools [C].
- Higher education: students should be aware of their microbiological status and are advised to discuss this with their CF physician, the student health service (which then has legal responsibility) and their personal tutor [C].
- Workplace: people with CF should be aware of their microbiological status and are advised to discuss this with their CF physician and occupational health services who can then take appropriate action to minimise the risk of cross-infection [C].
- Siblings with CF should have separate bedrooms and should perform their airway clearance and other treatments separately [C].

13. Risks of various forms of social contact

The exact risk associated with each different type of social contact is unknown and depends on the likelihood of transferring respiratory secretions. It would be wrong to deliberately expose patients to Bcc to find out. However, it is known that the risk of being infected increases with closer types of contact, with the duration of contact and when strains with known epidemic potential, such as

B. cenocepacia ET12, are involved. The degree of risk associated with some typical situations can be estimated. Contacts that do not last very long, or do not occur very often, are less risky than contacts, which are prolonged or frequent. Outdoor events are thought to be less risky than indoor events provided good hygiene is observed.

13.1 Table: Activities shared with other people with cystic fibrosis: Risk of transmission

Brief encounters indoors or outdoors	Low
Closer social contact – evenings in the pub or restaurant	High
Hand shaking	High
Contacts involving siblings with cystic fibrosis	High
Sharing bedrooms	High
Social kissing	High
Travelling together in closed conditions e.g. car or lift	High
Sports or exercise classes	High
Sharing eating or drinking utensils	High
Intimate contact - kissing, sexual relationships	High

14. References

In addition to the references cited, readers are directed to additional information and updates on the Bcc to be found on the website of the International Burkholderia cepacia Working Group (http://go.to/cepacia).

There are wide-ranging reviews covering taxonomy, epidemiology, virulence, clinical management and biopesticide use (Govan et al, 1996 [IV]; LiPuma, 1998 [IV]; Speert 2002 [IV]; Mohr et al, 2001 [IV]; Moore & Elborn, 2001 [IV]; Jones, et al, 2001b; [IV]; Coenye et al, 2001b [IV]; Environmental Protection Agency U.S. 2002, [IV]). Guidelines on infection control for Bcc infection are also contained within the comprehensive Society for Healthcare Epidemiology of America [HEA] document (Saiman et al, 2003 [IV]) and a recent review (Saimon & Siegel, 2004). The limited options for antibiotic therapy can be found in Antibiotic Treatment for Cystic Fibrosis (Cystic Fibrosis Trust, 2002 [IV]).

NB. Pseudomonas cepacia is now named Burkholderia cepacia. Papers prior to 1995 refer to Pseudomonas cepacia.

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Notes

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The Cystic Fibrosis Trust is the only UK-wide charity dedicated to fighting for a life unlimited by cystic fibrosis (CF) for everyone affected by the condition. Our mission is to create a world where everyone living with CF will be able to look forward to a long, healthy life.

At the Trust we are:

- Investing in cutting-edge research
- Driving up standards of clinical care
- Providing support and advice to people with CF and their families
- Campaigning hard for the issues that really matter

Fighting for a Life Unlimited